Skin sensitization risk assessment: considering available data for weight of evidence assessments

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We would like to thank Basketter and Safford (2016) for their excellent article concerning the scientific basis for assessment factors (AFs) used in quantitative risk assessment (QRA) for dermal sensitizers. We believe their article provides critical support for the QRA methodology.

Basketter and Safford discuss estimating acceptable exposure levels based on data from human testing or from the Local Lymph Node Assay (LLNA), which is clearly the test that should be conducted for new chemicals or chemical registrations. However, LLNA data are not available for many existing chemicals which may nonetheless need to be evaluated under time and budgetary circumstances where new testing may not be feasible, e.g., cases of product adulteration, emergency release scenarios, or first pass screening for chemical alternatives assessment. In the absence of test data, Safford *et al*. (2015) proposed a dermal sensitization threshold (DST) of 64 $\mu g/cm^2$ for chemical sensitizers not identified as high potency agents. But how should one address cases where data other than LLNA results for the chemical of interest are already available?

Much of the data contained in repositories such as the European Chemicals Agency (ECHA) database come from studies completed prior to the development of the LLNA, with the guinea pig maximization test (GPMT) and Buehler assay predominating. These tests are typically conducted with a single induction dose and are aimed at identifying sensitizing hazard rather than sensitization potency. Even with these limitations, and lacking better data, it may be insightful to apply guinea pig data, with "judicious interpretation" (Kimber *et al*. 2001) in risk assessment. A review of dose-response data from several multi-dose GPMT studies (Stadler and Karol, 1985; Andersen *et al*. 1995; Wahlkvist *et al*. 1999; Frankild *et al*. 2000; van Och *et al*. 2001; Yamano *et al*. 2005) suggests that an AF of 10 or 30 could be used to derive a conservative estimate of a threshold for chemicals that produce only limited sensitization at the top induction tested dose (*e.g.*, consistent with Magnusson and Kligman's weak, mild and moderate categories). As the GPMT involves both intradermal and epicutaneous induction exposures, consideration of the potential impact of skin barrier function would also be appropriate as noted in Basketter *et al*. (1997). Data for the Buehler assay, which are more limited, suggest a factor of 10 could be used (although the Buehler assay may not detect weak sensitizers). For chemicals where the top tested dose produces higher levels of sensitization (*e.g.,* 80-90%) or which provoked extreme severity of response, an AF of 100 may be more appropriate to apply to the test concentration to conservatively estimate an induction threshold dose. Lastly, it may be critical to note the uncertainty involved in such an extrapolation and perhaps discuss the results in relation to the DST as part of a weight of evidence evaluation.

A second source of information for a weight-of-evidence evaluation relates to “read across” from data for structurally similar chemicals. Again, it may be helpful in cases where data on a particular chemical of interest are lacking and yet some assessment of safety is required in a timeframe or budgetary constraint where additional study is not possible. Data for carefully selected surrogates considering properties relevant to the adverse outcome pathway (AOP) can be used to predict sensitization risk, again with the use of appropriate AFs. We have used AFs of 1 or 3 for very close surrogates (e.g., chemicals with a single additional carbon atom in a non-reactive side chain, different salts of fatty acid esters, chemicals where other empirical data support similar potency) and AFs of 5 or 10 where

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surrogates are further apart (e.g., chemicals possessing identical reactive functional groups but somewhat different carbon backbones). Transparency, objectivity and adequate documentation in the selection of surrogates is vital in such cases as is an openness to determining that no adequate surrogate with data exists. This is consistent with other proposed approaches for facilitating consistency in the surrogate selection process while also accounting for uncertainty associated with that selection in any subsequent quantitative risk assessment (Blackburn and Stuard 2014; Ball *et al*. 2016).

Dermal sensitization is a growing health concern. We have found the QRA methodology to be a robust approach for addressing such concerns but have also found it is unable to use all of the available data currently in hand for addressing skin sensitization. While it is clear that optimal test methods (*e.g.*, the LLNA) should be used to obtain data for new chemicals or chemicals being introduced in ways that will provide widespread exposure, there are situations where such testing is infeasible. We believe that incorporation of other data into the QRA process with appropriate AFs can help address these situations in ways that are informative.

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